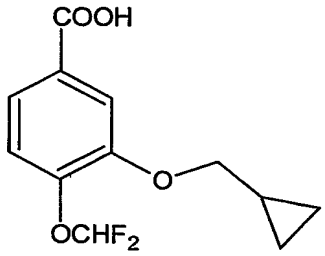
PROCESS FOR THE PREPARATION OF ROFLUMILAST

Field of the Invention

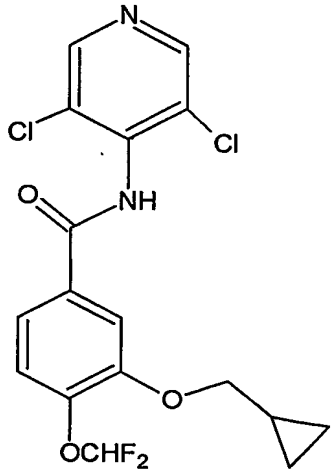
The field of the invention relates to a process for the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid of Formula I, and to the use of this compound as an intermediate for the preparation of roflumilast.



FORMULA I

Background of the Invention

Chemically, roflumilast is 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)benzamide of Formula VI, and is known from U.S. Patent No. 5,712,298.



FORMULA VI

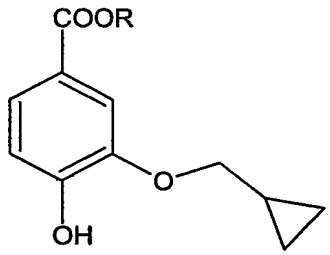
Roflumilast is an effective phosphodiesterase-4-inhibitor (PDE4-inhibitor), which can be used in the treatment of asthma, inflammation, bronchitis, allergy, osteoporosis, dermatoses and disorders related to immune system, heart and kidney.

U.S. Patent No. 5,712,298 discloses the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid comprising reacting 4-hydroxy-3-cyclopropylmethoxybenzaldehyde with dichlorofluoromethane followed by oxidation.

U.S. Patent No. 6,712,274 discloses the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid comprising reacting dihydroxybenzaldehyde with tertiarybutyl difluorochloroacetate in the presence of lithium carbonate and reacting the obtained 4-difluoromethoxy-3-hydroxy benzaldehyde with cyclopropylmethyl bromide in the presence of potassium carbonate followed by oxidation to yield 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid.

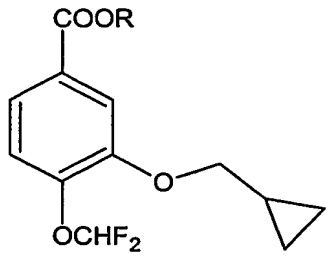
Summary of the Invention

In one general aspect there is provided a process for the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid. The process includes reacting the compound of Formula II,



FORMULA II

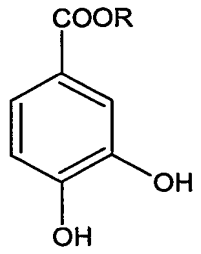
wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl, with difluoro methylating agent in the presence of a base to obtain compound of Formula III,



FORMULA III

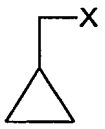
wherein R is as defined above; and desterification of the compound of Formula III to obtain the compound of Formula I.

In another general aspect there is provided a process for the preparation of 3-cyclopropylmethoxy-4-hydroxy benzoate of Formula II. The process includes reacting 3,4-dihydroxy benzoate of Formula IV,



FORMULA IV

wherein R is as defined above, with cyclopropylmethyl derivative of Formula V,



FORMULA V

wherein X is a leaving group, in the presence of a base.

In another general aspect there is provided a novel compound, 3-cyclopropylmethoxy-4-hydroxy benzoate of Formula II.

In another general aspect there is provided a novel compound of Formula III.

In another general aspect there is provided a process for the preparation of roflumilast. The process includes reacting compound of Formula I with 4-amino-3,5-dichloro pyridine.

In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of roflumilast; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have developed an efficient process for the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid. The process involves reacting the

compound of Formula II, wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl, with difluoro methylating agent in the presence of a base to obtain compound of Formula III, wherein R is as defined above; and desterification of the compound of Formula III to obtain the compound of Formula I.

Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, secondary butyl and tert- butyl groups. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl and hexenyl groups. The substituted phenyl includes phenyl substituted by 1-3 substituents, which are independently bromine, chlorine, fluorine, C_1-C_4 alkyl, C_1-C_4 alkoxy, and nitro groups. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy and butoxy groups. The substituted benzyl includes p-nitro benzyl, p-methoxy benzyl, o-nitro benzyl, p-bromo benzyl, and 2,4,6-trimethyl benzyl groups.

The difluoro methylating agent which can be used for preparing 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid of Formula I include difluorochloromethane (Freon-22®), alkyl difluorochloroacetate such as methyl difluorochloroacetate, ethyl difluorochloro acetate and tertiarybutyl difluorochloroacetate.

The bases which can be used include organic and inorganic bases. Examples of organic bases include trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, DBU (1,8-diazabicyclo- [5.4.0]-undec-7-ene), DBN (1,5-diazabicyclo-[4.3.0]-non-5-ene), 4-dimethylamino pyridine and mixtures thereof. Examples of inorganic bases include alkali metal carbonate, bicarbonate, hydroxide and mixtures thereof. Examples of alkali metal carbonates include lithium carbonate, sodium carbonate and potassium carbonate. Examples of alkali metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of alkali metal hydroxides include sodium hydroxide and potassium hydroxide.

The reaction of compound of Formula II with difluoromethylating agent may be carried out in the presence of phase transfer catalyst. Examples of such phase transfer catalysts include quaternary ammonium salts such as tetramethyl ammonium iodide, tetrabutyl ammonium iodide, benzyltributyl ammonium bromide, 1-methylpyridinium iodide, tetramethyl-2-butylammonium chloride, trimethylcyclopropylammonium

chloride, tetrabutylammonium bromide and t-butylethyldimethylammonium bromide; quaternary phosphonium salts such as tributylmethylphosphonium iodide, triethylmethylphosphonium iodide, methyltriphenoxyphosphonium iodide, tetrabutyl phosphonium bromide, benzyltriphenyl phosphonium bromide, and tetraphenyl phosphonium chloride.

The reaction of compound of Formula II with difluoromethylating agent may be carried out in the presence of a suitable solvent. Suitable solvents are inert organic solvents that do not change under the reaction conditions. Examples of such solvents include alkyl ethers such as diethylether, diisopropylether and dimethoxyethane; nitriles such as acetonitrile and benzonitrile; alcohols such as methanol, ethanol, isopropanol and butanol; ketones such as acetone and methyl isobutyl ketone; chlorinated hydrocarbons such as methylene chloride, ethylene dichloride and carbon tetrachloride; esters such as ethylacetate and isopropylacetate; hydrocarbons such as benzene, xylene, toluene , hexane, cyclohexane, heptane and octane; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; cyclic ethers such as dioxane and tetrahydrofuran, and mixtures thereof.

The reaction may be carried out at a temperature of from about 20°C to about 120°C, for example at a temperature of from about 25°C to about 50°C.

The compound of Formula III is converted to the compound of Formula I by conventional methods including hydrolysis or hydrogenation, in case R is a benzylic group.

Examples of leaving group X, in the compound of Formula V, include chlorine, bromine, iodine, sulphate and tosylate.

The base, phase transfer catalyst and solvent, which may be used for preparing 3-cyclopropylmethoxy-4-hydroxy benzoate of Formula II from compound of Formula IV, can be the same as those which can be used in reaction of compound of Formula II with difluoromethylating agent.

The reaction may be performed at a temperature from about 20°C to about 120°C. In particular, it may be performed at a temperature from about 25°C to 50°C.

In general, roflumilast of Formula VI is prepared by reacting an activated derivative of the acid of Formula I, such as acid halide or a reactive ester, with 4-amino-3,5-dichloro pyridine. For example, roflumilast can be prepared by reacting the

corresponding acid chloride of the compound of Formula I with 4-amino-3,5-dichloro pyridine in the presence of sodium hydride in tetrahydrofuran.

The resulting roflumilast may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The compositions include dosage forms suitable for oral, buccal, rectal, and parenteral (including subcutaneous, intramuscular, and ophthalmic) administration. The oral dosage forms may include solid dosage forms, like powder, tablets, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions, emulsions, pastes and elixirs. Parenteral dosage forms may include intravenous infusions, sterile solutions for intramuscular, subcutaneous or intravenous administration, dry powders to be reconstituted with sterile water for parenteral administration, and the like.

The roflumilast can be administered for the treatment the treatment of asthma, inflammation, bronchitis, allergy, osteoporosis, dermatoses and disorders related to immune system, heart and kidney in a warm-blooded animal.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

In the following section embodiments are described by way of examples to illustrate the process of invention. However, these do not limit the scope of the present invention. Variants of these examples would be evident to persons ordinarily skilled in the art.

Example 1: Preparation of 3-Cyclopropylmethoxy-4-hydroxy methyl benzoate

3,4-Dihydroxy methyl benzoate (50 g) was stirred with cyclopropylmethyl bromide (50.2 g) and potassium carbonate (82.1 g) in acetone (350 ml) for 18 hours at 40°C. The reaction mixture was filtered over a hyflo bed followed by concentration of the organic layer.

The crude product was purified over a silica gel column (eluting with 5 % ethyl acetate in hexane) to obtain the title product.

Yield: 16 g.

HPLC Purity: 99.5%

Example 2: Preparation of 3-Cyclopropylmethoxy-4-difluoromethoxy benzoic acid

The product obtained from Example 1 (10 g) was subjected to difluoromethylation using difluorochloromethane, 35 % w/w sodium hydroxide aqueous solution (50 ml), tetrabutyl ammonium bromide (5.9 g) in toluene (100 ml) as solvent at 20 to 35° C. The resulting product, 3-cyclopropylmethoxy-4-difluoromethoxy methyl benzoate was hydrolyzed *in situ* by adding 50 ml water and heating the reaction mixture to 50 to 55°C. pH of the reaction mixture was adjusted to 3-4 by adding concentrated hydrochloric acid at 20 to 30°C followed by extraction with ethyl acetate (48 ml) .The solvent was evaporated under vacuum and the product was collected.

Yield: 10 g.

HPLC Purity: 94.0%

Example 3: Preparation of roflumilast

The product obtained from Example 2 (10g) was heated with thionyl chloride (5.8g) and catalytic amount of dimethylformamide (0.5ml) at 80 to 85°C for 1 hour. The solution was evaporated *in vacuo* and the oily residue was dissolved in dry tetrahydrofuran (50 ml). This was added dropwise at 0°C to a suspension prepared from sodium hydride (3.75 g, 60% suspension) and 4-amino-3,5-dichloro pyridine (9.5g) in dry tetrahydrofuran (50 ml) with stirring. The reaction mixture was stirred for 30 minutes and then acidified to pH 2 with hydrochloric acid (1 N). The reaction mixture was extracted with ethyl acetate. The extracted solvent was washed with sodium bicarbonate solution (5%) and water followed by evaporation in vacuum. The residue was dissolved in methanol (45 ml) at 60°C and 5 ml of water was added to get precipitate. The mixture was then cooled to 10°C and filtered to obtain roflumilast.

Yield: 9.2 g

Purity: 99%

m.p.: 157-158°C

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.